REMARKS

The Added Claims

To advance prosecution, applicants have cancelled all of pending claims 1-83 and substituted new claims 84-91.

Claims 84-91 do not constitute new matter. They read on the elected Infliximab crystals. They simplify the issues in the case. They overcome the outstanding rejections. Their entry is requested.

Claim 84 is directed to a crystal of the antibody Infliximab. It is supported, for example, by original claim 13. *See also* Figures 2 and 7 and Examples 34-37.

Claim 85 is directed to a pharmaceutical composition characterized by a specific minimum antibody concentration (about 20 mg/ml). *See, e.g.*, original claims 26-30 and page 53, line 7 – page 54, line 2.

Claims 86-90 are directed to large-batch crystallization methods. *See, e.g.*, original claims 43-68 and 74-75 and Examples 1-37.

Claim 91 is directed to antibodies produced by the large-batch crystallization method of claims 86-90. *See* above and *see* added claim 79 and specification, page 67, line 23 – page 75, line 5.

The Rejections

Former product claims 1, 5-6, 9-11, 21-25, 31 and 33 remain rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Harris. Applicants traverse.

Claims 84, 85 and 91, all product claims, are not anticipated by Harris for the same reason that former product claim 13 (specific antibody), claim 26 (specific antibody concentration) and claim 79 (antibody produced by the large-batch crystallization method of the invention) were not anticipated. Harris describes none of those products.

Former product claims 2, 6, 11, 20-24 and 32 remain rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by Hoedemaeker. Applicants traverse.

Claims 84, 85 and 91, all product claims, are not anticipated by Hoedemaeker for the same reason that former product claim 13 (specific antibody), claim 26 (specific antibody concentration) and claim 79 (antibody produced by the large-batch crystallization method of the invention) were not anticipated. Hoedemaeker describes none of those products.

Former method and product by process claims 43-68 and 74-75 remain rejected and claim 79 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Harris in combination with McPherson, and further in view of Pollack. Applicants traverse.

Method claims 86-90 and product by process claim 91 are patentable over any combination of Harris, McPherson or Pollack. These claims are directed to applicants' inventive method of the large-batch crystallization of antibodies.

Antibodies, which are very complex macromolecules, are difficult to crystallize. The few examples of such crystallizations have been on the very small micro scale for the purpose of x-ray crystallography studies. *See, e.g.*, Harris. Crystallization on a large scale is difficult.

Applicants have solved this problem and have developed a large batch method to crystallize antibodies. Applicants' invention first involved their recognition that crystallization conditions determined using the traditional and classical micro techniques of vapor diffusion, free interface diffusion, or micro dialysis were not generally useful in large-batch crystallization of antibodies.

As reflected in claims 86-91 and as compared to those classical screening methods, applicants' method employs micro-batch crystallizations to select crystallization buffers that are useful in their large-batch crystallization methods. *See, e.g.*, Examples 1-37. As also reflected in claims 86-91, applicants' method uses agitation (about 3-48 hours) and temperatures (about -21°C-61°C) to produce the antibody crystals in their large batch methods using the selected buffers.

Harris refers to the crystallization of antibodies for x-ray crystallography. To determine appropriate crystallizations conditions, Harris refers to using the "sitting drop" vapor diffusion method and refers to McPherson. *See* page 286.

McPherson refers to various "micro techniques" to screen for appropriate crystallization conditions. These include vapor diffusion -- "handing drop" or "sitting drop". *See, e.g.*, pages 8-9 and Figure 9.

While each of these prior art micro crystallization screening techniques is based on changing various conditions in the crystallization solution, none provides conditions that are easily or with good fidelity transferred to large-batch crystallization methods. And, such screening methods have never been transferred to the large-batch crystallization of antibodies.

Indeed McPherson notes that even its micro techniques themselves may reach very different end points. For example, while the equilibrium principle of both the sitting drop and hanging drop methods are very similar, the results maybe very different (page 11):

> In some cases there are striking differences in the degree of reproducibility, final crystal size, morphology, required time or the degree of order. These observations illustrate the important point that the pathway leading to super-saturation, the kinetics of the process may be as important as the final product achieved.

Further, none of Harris, McPherson or Pollack describes or suggests using applicants' micro-batch techniques to determine appropriate large scale crystallization conditions for antibodies. Without such disclosure, these prior art documents, in fact, teach away from applicants' claimed invention. They teach only the classical micro techniques for choosing crystallization conditions.

For all of these reasons, method claims 86-90 and product by process claim 91 are patentable over Harris, McPherson or Pollack.

The specification stands objected to for its use of a variety of trademarks, *e.g.*, page 81, line 28 and page 96, line 5. Applicants traverse.

Applicants use of the trademarks Rituxan™ and Herceptin™ are proper use of those marks. *See* MPEP § 608.01(v). They are first letter capitalized and marked with the trademark symbol. Applicants have also described the product to which the mark is used to identify the commercial embodiment. *See, e.g.*, page 81, line 27 – page 82, line 5.

> [0227]Rituximab is a chimeric murine/human monoclonal antibody commercially available as Rituxan™ (Genentech, Inc., South San Francisco, CA). This monoclonal antibody

> has been widely used to treat non-Hodgkin's lymphoma. Rituximab is a chimeric IgG1 kappa immunoglobulin that binds to the CD20 antigen on the surface of normal and malignant B-lymphocytes. It is composed of murine light- and heavy-chain variable region sequences and a human constant region sequence. The Rituximab antibody has an approximate molecular weight (MW) of 145 kD.

For these reasons, applicants request that the Examiner reconsider and withdraw the objection to the specification.

Former product claims 1, 3, 4, 11, 13, 15-34 and 39 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. Applicants traverse.

Applicants have cancelled claims 1-3. The Examiner pointed to those claims as the sole reason for his rejection of all of the other claims. The rejected language is not present in the pending product claims 84, 85 and 91.

Former claims 1-3, 5-11, 15-34, 39, 43-68, 70-71, 74-76, 79-80 and 82-83 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse.

Claims 84-91 are directed to "antibodies", not fragments of antibodies. Thus, those claims are supported by the written description which, as the Examiner has acknowledged, describes crystals of three antibodies. The specifically described antibodies vary in both their structure and function. Thus, their written description satisfies the case law cited by the Examiner as supporting a genus claim to antibody crystals.

Former product claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Margolin et al., WO 99/55310 ("Margolin"). Applicants traverse.

Claims 84-91 are not anticipated by Margolin for the same reason that original claim 13 (specific antibody), claim 26 (specific antibody concentration) and claim 43 (large-batch method) were not anticipated by Margolin. Margolin does not describe the products or methods of any of these claims.

Former product or kit claims 1, 3, 5, 17-18 and 70-71 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Navia et al., United States patent 5,849,296 ("Navia"). Applicants traverse.

Claims 84-91 are not anticipated by Navia for the same reason that original claim 13 (specific antibody), claim 26 (specific antibody concentration) and claim 43 (large-batch method) were not anticipated by Navia. Navia does not describe the products or methods of any of these claims

Former product claims 1, 5-11, 13, 15-16, 19-34, 39, 76 and 80 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Margolin and further in view of Remicade, Package Insert (August 1998) ("Package Insert"). Applicants traverse.

Claims 84 and 85 are not obvious in view of Margolin and the Package Insert for the reasons that Margolin teaches stabilized crystals and methods to stabilize crystals. The Examiner pointed to the advantages of crystals as listed on pages 8-10 of Margolin. Margolin, however, continues: "The present invention overcomes the above-described obstacles by employing the most stable form of an active protein, the

crystalline form and either (1) adding ingredients or excipients where necessary to stabilize dried crystals or (2) encapsulating the protein crystals ..." (page 10, lines 19-24). The present invention teaches, on the other hand, crystallized antibodies before they are stabilized further by Margolin.

CONCLUSION

In view of the above claim amendments and arguments, applicants request that the Examiner consider claims 84-91 and allow them. Should the Examiner believe that any remaining issues can be resolved by telephone conference, the Examiner is invited to telephone the undersigned at any time.

Respectfully submitted,

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